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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/808,827	02/28/1997	WALTER HENRY GUNZBURG	2316.1001-000	6837

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EXAMINER	
BRUSCA, JOHN S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 10/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/808,827	GUNZBURG ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,7,9-26,28,29 and 31-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,7,9-26,28,29 and 31-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02 September 2004 has been entered.

Claim Rejections - 35 USC 112

2. The rejection of claims 1, 5, 7, 9-26, 28, 29, 31, 32, and 56-78 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement in the Office action mailed 02 March 2004 is withdrawn in view of the amendment to claims 1, 17, 28, 56, 66, and 74 filed 02 September 2004 deleting the phrase "which is not related to a promoter from a retrovirus upon which the retroviral vector is based."

3. The rejection of claims 1, 5, 7, 9-26, 28, 29, 31, 32, and 56-78 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention in the Office action mailed 02 March 2004 has been withdrawn in view of the amendment to the claims in the amendment filed 02 September 2004.

Claim Rejections - 35 USC 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al.

Couture et al. (Reference AS in the Form PTO-1449 filed 9/23/97) shows retroviral vectors comprising a substitution of a portion of the 3' U3 region with the corresponding region of 5 different murine retroviruses, including leukemia and sarcoma retroviruses. Couture et al. shows on page 669 column 2 that the first 40 nucleotides of the original vector are retained in the substitution of the U3 region. The vector of Couture comprises a chloramphenicol acetyl transferase marker gene and a neomycin resistance gene. Couture et al. shows in the abstract that after packaging, the substituted U3 region appears at the 5' LTR and serves as a promoter for all genes in the body of the vector, and that different LTR constructs were preferentially expressed in specific cell types. Couture et al. states in the second paragraph of the Results section on page 669 that U3 regions are bound by cellular factors. Couture et al. shows in Table 3 that their

chimeric LTR promoters are active in a cell type specific manner. Couture et al. state on page 670 that promoter suppression or interference may occur within retroviral vectors containing internal promoter elements. Couture et al. states on page 667 that retroviral vectors with target cell specificity have utility in gene therapy protocols. Couture et al. shows the use of packaging cell lines PA317 and GP&E86 on page 669 to package their retroviral vectors. Couture et al. does not show a vector comprising a multiple cloning site in the U3 region.

Faustinella et al. shows in figure 1 Moloney murine leukemia retroviral vector pS3. pS3 comprises a partial deletion of the 3' U3 region, into which has been inserted a polylinker with unique cloning sites, for example the Bsa AI site and the Nae I site used to construct the vectors of figure 2.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vectors of Couture et al. by adding the multiple cloning site of Faustinella et al. because Faustinella et al. shows that multiple cloning sites may be used to insert sequences of choice in a U3 region of a retroviral vector.

6. Claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mee et al.

Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above does not show mouse mammary tumor virus (MMTV) promoters or regulatory elements.

Mee et al. shows a retroviral vector comprising a mouse mammary tumor virus LTR, and that the LTR expressed a gene after induction with dexamethasone. Mee et al. state on page 292 that their vector is a potentially powerful tool for the manipulation of gene expression in a variety of cell types.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above by insertion of an MMTV promoter region in a deleted 3' U3 region of a retroviral vector because Mee et al. show that their LTR promoter may be used to manipulate gene expression in a variety of cell types.

7. Claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-36, 38, 39, 42-49, and 51-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mehigh et al.

Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above does not show cellular promoters or regulatory elements.

Mehigh et al. shows a retroviral vector comprising a whey acidic acid protein (WAP) promoter. Mee et al. states in the abstract that their vector allows for inducible expression from the WAP promoter of an operably linked gene in MBDK cells and may prove useful as a delivery system for peptides in cattle to increase milk production.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above by insertion of a WAP promoter region in a deleted 3' U3 region of a retroviral vector because Mehigh et al. shows that such vectors are inducibly expressed and may allow for increased milk production in cattle.

8. Claims 1, 13, 14, 33, 40, 41, 56, 63, and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of:

1)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above,

2)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mee et al. as applied to claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78,

3) Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mehigh et al. as applied to claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-35, 38, 39, 42-49, and 51-55;

where each of the above three are as evidenced by Miller et al. and Panganiban et al.

The three combinations of references cited above do not explicitly show an altered retroviral gene or a partially deleted sequence involved in integration of retroviruses.

Couture et al. shows in figure 1 a retroviral vector LCSN and a derivative of LCSN. Couture et al. shows in the Methods section on page 668 that their vectors are derivatives of the vectors of Miller et al.

Miller et al. shows in figure 2 that their vectors retain the phi+ packaging sequence, but lack the gag, pol, and env genes of a replication-competent retrovirus.

Panganiban '84 shows that the 3' end of the pol gene encodes the int locus that is required for integration of the reverse transcribed retroviral genome to form a provirus.

Therefore the vectors of claims 13 and 14 are taught by the above cited combinations of references as evidenced by Miller et al. and Panganiban et al.

9. Claims 1, 10, 33, 37, 56, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of:

1)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above,

2)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mee et al. as applied to claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78,

3) Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mehigh et al. as applied to claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-35, 38, 39, 42-49, and 51-55;

where each of the above three are further in view of Price et al.

The three combinations of references cited above do not explicitly show retroviral vectors derived from BAG vectors.

Price et al. shows a BAG retroviral vector comprising a beta galactosidase reporter gene, and that the vector can be used to identify cells and progeny of cells infected with the vector.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of the above cited combinations of references by basing the construction on a BAG vector of Price et al. because Price et al shows that a vector with a beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector.

10. Claims 17, 20, 21, 26, 28, 43, 50, 51, 52, 53, 66, 73, 74, 75, and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of:

1)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above,

2)Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mee et al. as applied to claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78,

3) Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 above, and further in view of Mehigh et al. as applied to claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-35, 38, 39, 42-49, 51-55, 79-82, 84, 85, 88-95, and 97-101;

where each of the above three are further in view of Longmore et al. and Kay et al.

The three combinations of references cited above do not show use of retroviruses in animals.

Longmore et al show in the abstract that mice infected with a retroviral vector expressing the erythropoietin receptor had increased platelet counts and splenic megakaryocytes.

Kay et al. shows in the abstract and throughout that hemophiliac dogs infected with a retroviral vector expressing factor IX shows improved levels of clotting and thromboplastin times for greater than 5 months after treatment.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the teachings of the combinations of references cited above to express a therapeutic protein because both Kay et al. and Longmore et al. show that retroviral vectors may be used to express therapeutically effective levels of a recombinant protein in an animal.

11. Applicant's arguments filed 02 September 2004 have been fully considered but they are not persuasive.

On page 26 and beyond in their arguments the applicants state that Couture et al. does not show a partially deleted U3 region. However Couture et al. shows a chimeric U3 region that was created by first deleting a portion of the original U3 region of the MuMLV based vector and substituting portions of U3 regions from six different murine leukemia viruses. Figure 3 of Couture et al. details the differences in sequence of the resulting U3 regions at the sequence level from the starting U3 region. On page 26 the applicants equate a deleted U3 region with an incomplete U3 region, however this is not correct and claims 1, 17, 28, 56, 66 do not require an incomplete or defective U3 region. Couture et al. first deleted a region of the original U3 region as required by claims 1, 17, 28, 56, 66 and then inserted a substitute sequence that restored function to the 3" LTR consisting of an LTR sequence from a different murine leukemia retrovirus. It is apparent that the applicants wish to claim a combined deletion/substitution LTR

in the mouse mammary tumor virus embodiment of claim 7 (as disclosed in the example of pages 21-22 of the instant specification).

The applicants state that Couture et al. does not provide motivation to use the polylinker of Faustinella et al. However Faustinella et al. provides motivation to use a polylinker in a 3' U3 region in other vectors because Faustinella et al. shows that such a polylinker can be used to provide convenient restriction endonuclease sites to allow for insertion of sequences that are expressed upon infection. Couture et al. shows use of restriction endonuclease sites to aid in construction of their deletion/insertion U3 region, and so the use of the polylinker is compatible with the purpose of Couture et al. in construction of recombinant U3 regions. The applicants further argue that Faustinella et al. teaches away from insertion of promoters into a U3 polylinker because Faustinella et al. inserts a promoter operably linked to a coding sequence. However the particular insert used by Faustinella et al. does not directly teach away from use of other inserts, such as the LTR promoter inserted into the U3 region by Couture et al.

The discussions of the rejections involving the Mee et al., Mehigh et al., Miller et al., Panganaban et al., Price et al., Longmore et al., and Kay et al. references are reiterative of the arguments concerning the Couture et al. and Faustinella et al. combination and have been addressed above.

Conclusion

12. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action

after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also

enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center at (800) 786-9199.Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward can be reached on 571 272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J.S. Brusca 23 October 2004

John S. Brusca
Primary Examiner
Art Unit 1631

jsb